General

Guideline Title

SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). SonoVue (sulphur hexafluoride microbubbles) â€“ contrast agent for contrast-enhanced ultrasound imaging of the liver. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Aug. 41 p. (Diagnostics guidance; no. 5).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Contrast-enhanced ultrasound with SonoVue is recommended for characterising incidentally detected focal liver lesions in adults in whom an unenhanced ultrasound scan is inconclusive. An unenhanced ultrasound scan in which a focal liver lesion is detected, but not characterised, is defined as inconclusive.

Contrast-enhanced ultrasound with SonoVue is recommended for investigating potential liver metastases in adults:

- If contrast-enhanced computed tomography (CT) is not clinically appropriate, is not accessible or is not acceptable to the person, and
- In whom an unenhanced ultrasound scan is unsatisfactory and contrast is needed for further diagnosis

Contrast-enhanced ultrasound with SonoVue is recommended for characterising focal liver lesions in adults whose cirrhosis is being monitored:

- If contrast-enhanced magnetic resonance imaging (MRI) is not clinically appropriate, is not accessible or is not acceptable to the person, and
- When unenhanced ultrasound scan is inconclusive

Clinical Algorithm(s)

An algorithm titled "Diagnostic Pathway for Liver Imaging with Contrast-enhanced Ultrasound as a Replacement for Contrast-enhanced

CT/contrast-enhanced MRI" is provided in the original guideline document.

Scope

Disease/Condition(s)

- Benign focal liver lesion
- Hepatocellular carcinoma (HCC)
- Liver metastases from colorectal cancer
- Cirrhosis of the liver

Guideline Category

Diagnosis

Evaluation

Technology Assessment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Oncology

Radiology

Surgery

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To compare the clinical and cost-effectiveness of contrast-enhanced ultrasound using the contrast agent SonoVue with contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) for investigating and characterising focal liver lesions in adults, in whom previous liver imaging has been inconclusive

Target Population

Adults with focal liver lesions in whom previous liver imaging has been inconclusive

Interventions and Practices Considered

Contrast-enhanced ultrasound imaging of the liver using SonoVue (sulphur hexafluoride microbubbles)

Major Outcomes Considered

- Effect of testing on the treatment plan (for example, surgical or medical management, or palliative care)
- Effect of pre-treatment testing on clinical outcome (for example, overall survival, progression-free survival)
- Prognosis – the ability of the test result to predict clinical outcome (for example, overall survival, progression-free survival, response to treatment)
- Test accuracy and number of people or lesions for which no conclusive diagnostic information could be obtained with contrast-enhanced ultrasound using SonoVue
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by Kleijnen Systematic Reviews Ltd. (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Inclusion and Exclusion Criteria

Participants

Study populations eligible for inclusion were: Adults (≥18 years) in whom previous liver imaging has been inconclusive, including patients being assessed for:

- Suspected primary hepatocellular carcinoma (HCC)
- Suspected secondary malignancy (liver metastases)
- Response to treatment/recurrence of known liver malignancy

Setting

Relevant settings were secondary or tertiary care.

Interventions

The intervention (index test) was SonoVue® contrast-enhanced ultrasound (CEUS).

Comparators

Comparators tests eligible for inclusion were:

- Contrast-enhanced computed tomography (CECT)

- Contrast-enhanced magnetic resonance imaging (CEMRI)

Reference Standard

Studies reporting the diagnostic accuracy of SonoVue® CEUS for the detection of liver malignancies were required to use histology, following biopsy or surgical excision, to confirm diagnosis in patients with positive index test results. Patients who test negative on the index test will generally not undergo biopsy or surgical treatment; clinical/radiological follow-up for a minimum of six months was therefore considered an acceptable reference standard in these patients.

Protocol Modification

The reference standard criteria were extended, for studies on the characterisation of focal liver lesions (FLLs) only (suspected HCC), to include studies which use European Association for the Study of the Liver (EASL)/American Association for the Study of Liver Diseases (AASLD) non-invasive diagnostic criteria (two concordant imaging test results) as the reference standard. This modification does not apply to test accuracy studies on the detection of liver metastases. This extension of the inclusion criteria was made because clinical opinion indicated that biopsy of small, test positive lesions may be considered unethical in this population and that the original criterion (biopsy for imaging test positive patients/lesions and 6 months follow-up for imaging test negative patients/lesions) may, therefore, result in important studies being excluded.

Outcomes

Studies reporting the following outcomes were considered relevant:

- Effect of testing on treatment plan (e.g., surgical or medical management, or palliative care), where information on the appropriateness of the final treatment plan is also reported
- Effect of pre-treatment testing on clinical outcome, (e.g., overall survival, progression free survival)
- Prognosis - the ability of test result to predict clinical outcome (e.g., overall survival, progression free survival, response to treatment)
- Test accuracy and number of patients/lesions classified as non-diagnostic by SonoVue® CEUS

For included studies reporting any of the above outcome measures, the following outcomes were considered, if reported:

- Acceptability of tests to patients or surrogate measures of acceptability (e.g., waiting time and associated anxiety)
- Adverse events associated with testing (e.g. claustrophobia, reaction to contrast media)
- Additional FLLs detected by CEUS, over and above those seen on un-enhanced ultrasound
- Radiation exposure was not considered a relevant outcome, as the population is mostly older adults in whom additional incident cancers due to imaging-related radiation are likely to be minimal. In addition a previous technology assessment (new generation CT for cardiac imaging) showed that including radiation exposure in modelling did not influence the results of cost-effectiveness analyses.

Study Design

The following study designs were eligible for inclusion:

- Randomised or non-randomised controlled trials, where participants are assigned to the intervention or comparator tests, for treatment planning, and outcomes are compared at follow-up.
- Observational studies which report the results of multi-variable regression modelling with clinical outcome (e.g., survival, response to treatment) as the dependent variable and index test result as an independent variable. Included studies should control adequately for potential confounders (e.g., age, tumour stage, previous treatment, results, of other imaging).
- Test accuracy studies, where the index test was compared with one or more of the comparators and the reference standard. Test accuracy studies of the index test alone were included where these were conducted in patients who had previously undergone one or more of the comparator tests (e.g., a study of the accuracy of SonoVue® for the diagnosis of HCC in patients with inconclusive findings on CECT).

Included test accuracy studies, were required to report the absolute numbers of true positive, false negative, false positive, and true negative index test results, or sufficient information to allow their calculation.

The following study/publication types were excluded:

- Pre-clinical and animal
- Reviews, editorials, and opinion pieces
- Case reports
- Studies reporting only technical aspects of the test, or image quality

- Studies with <10 participants

See Section 4.1 of the DAR for additional information on inclusion/exclusion criteria.

Search Strategy

Search strategies were based on target condition and intervention, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.

The following databases were searched for relevant studies from 2000 to September/October 2011:

- MEDLINE (2000-2011/09/wk 4) (OvidSP)
- MEDLINE In-Process Citations and Daily Update (2000-2011/10/05) (OvidSP)
- EMBASE (2000-2011/wk 39) (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library Issue 10:2011) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 4:2011) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (2000-2011/10/06) (via Cochrane Library)
- Health Technology Assessment Database (HTA) (2000-2011/10/06) (via Cochrane Library)
- Database of Abstracts of Reviews of Effects (DARE) (2011/01/01-2011/10/06) (CRD website)
- Health Technology Assessment Database (HTA) (2011/01/01-2011/10/06) (CRD website)
- Science Citation Index (SCI) (2000-2011/10/06) (Web of Science)
- National Institute for Health Research (NIHR) Health Technology Assessment (HTA) (2000-2011) (Internet)

See Section 4.2 in the DAR for the list of resources for supplementary searches and electronic searches for conference abstracts.

Searches were undertaken to identify studies of Sonovue®/sulphur hexafluoride CEUS in the diagnosis of liver cancer (primary and metastases). The main EMBASE strategy for each set of searches was independently peer reviewed by a second information specialist, using the PRESS-EBC checklist. Search strategies were developed specifically for each database and the keywords associated with liver cancer (primary and metastases) were adapted according to the configuration of each database. Searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in Appendix 1 in the DAR.

Identified references were downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles were checked for additional studies.

Inclusion Screening

Two reviewers independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant, after discussion, were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in Appendix 5 in the DAR.

Studies listed in submissions from the manufacturer of SonoVue®, Bracco UK Ltd, were first checked against the project reference database, in Endnote X4; any studies not already identified by our searches were screened for inclusion following the process described above. Studies referenced by manufacturers and excluded at the full paper screening stage are noted in Appendix 5 in the DAR. Appendix 5 also includes a list of studies, referenced by manufacturers, which were excluded at title and abstract screening.

Where there was insufficient information for full inclusion assessment, study authors were contacted for clarification.

Assessment of Cost-effectiveness

Search Strategy

Searches were undertaken to identify cost-effectiveness studies of ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) in the diagnosis of liver cancer. As with the clinical effectiveness searching, the main EMBASE strategy for each set of searches was independently peer reviewed by a second information specialist, using the PRESS-EBC checklist. Search strategies were developed specifically for each database and searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in Appendix 1 in the DAR.

The following databases were searched for relevant studies from 2000 to present:

- MEDLINE (2000-2011/09/wk4) (OvidSP)
- MEDLINE In-Process Citations and Daily Update (2000-2011/10/10) (OvidSP)
- EMBASE (2000-2011/wk 40) (OvidSP)
- National Health Service Economic Evaluation Database (NHS EED) (2000-2011) (via Cochrane Library)
- NHS EED (2011/01/01-2011/10/12) (CRD website)
- Health Economic Evaluation Database (HEED) (2000-2011/10/12) (Wiley) http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- Science Citation Index (SCI) (2000-2011/10/07) (Web of Science)

See Section 5.1 in the DAR for supplementary research sources.

Identified references were downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles were checked for additional studies.

Number of Source Documents

Assessment of Clinical Effectiveness

The literature searches of bibliographic databases identified 854 references. After initial screening of titles and abstracts, 175 were considered to be potentially relevant and ordered for full paper screening. No additional papers were ordered based on screening of the industry submission; all studies submitted had already been identified by bibliographic database searches. No additional studies were identified from searches of clinical trials registries. Figure 3 in the Diagnostics Assessment Report (DAR) (see the "Availability of Companion Documents" field) shows the flow of studies through the review process, and Appendix 5 in the DAR provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage.

Based on the searches and inclusion screening, 19 publications of 18 studies were included in the review. Hand searching of conference proceedings resulted in the inclusion of a further three studies, which were published in abstract form only. A total of 21 studies in 22 publications were, therefore, included in the review.

Assessment of Cost-effectiveness

- The Assessment Group screened 1194 titles and abstracts, from which they selected 40 papers. After full paper screening they excluded 36 studies and kept 4, which matched the inclusion criteria of an economic analysis which related to SonoVue®.
- Three separate models were used to assess the cost-effectiveness of contrast enhanced ultrasound using the contrast agent SonoVue®:
  - A cirrhosis surveillance model
  - A liver metastases of colorectal cancer model
  - An incidentally detected focal liver lesions (FLL) model

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by Kleijnen Systematic Reviews Ltd. (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Data Extraction

Data were extracted on: study details (study design, participant recruitment, setting, funding, stated objective, and clinical indication for testing relevant to this assessment for which data were reported); study participants (total number of participants and total number of focal liver lesions (FLLs), study inclusion criteria, study exclusion criteria, participant age and gender distribution, participant characteristics relevant to liver cancer risk, lesion size, and final diagnoses); details of index test, comparator(s) and reference standard (technical details of the test, details of who interpreted tests and how, threshold used to define a positive test); study results. All but one of the studies included in the review were diagnostic test accuracy (DTA) studies and the results extracted for these studies were: unit of analysis (patient or lesion); numbers of true positive, false negative, false positive and true negative test results; numbers of patients, or lesions classified as non-diagnostic by SonoVue® contrast-enhanced ultrasound (CEUS) and or comparator(s). The remaining study was a controlled trial which compared assessment with conventional imaging (contrast-enhanced computed tomography [CECT] or contrast-enhanced magnetic resonance imaging [CEMRI]) plus unenhanced ultrasound (US) to assessment with conventional imaging (CECT or CEMRI) plus SonoVue® CEUS prior to radiofrequency ablation (RFA); data were extracted from this study to calculate odds ratios (ORs) and mean differences for dichotomous and continuous patient-relevant outcomes, respectively. Data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second; any disagreements were resolved by consensus. Chinese language studies were extracted by one reviewer working with a native speaker and the only German language study was extracted by one reviewer and checked by a second. Full data extraction tables are provided in Appendix 4 in the DAR.

Quality Assessment

The evidence-based Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool is recommended for assessing the methodological quality of test accuracy studies. A revised version of QUADAS (QUADAS-2) has recently been published (www.QUADAS.org). QUADAS-2 more closely resembles the approach and structure of the Cochrane risk of bias tool. A modified version of the QUADAS-2 tool, which includes an additional domain for the comparator test and additional signalling questions in the 'flow and timing' domain, has been used in this assessment. Review-specific guidance was produced for the use of the modified version of QUADAS-2 and is reported in Appendix 2 in the DAR.

The results of the quality assessment are summarised and presented in tables and graphs in Section 4.6 in the DAR and are presented in full, by study, in Appendix 3 in the DAR. No diagnostic accuracy data set included in this assessment was of sufficient size to allow statistical exploration of between study heterogeneity based on aspects of risk of bias. The findings of the quality assessment were used to inform recommendations for future research. The risk of bias in the controlled clinical trial was assessed using a table based on the Cochrane Collaboration's tool for assessing risk of bias.

Methods of Analysis/Synthesis

The results of DTA studies included in this review were summarised by clinical indication for imaging (characterisation of FLLs detected on routine surveillance of cirrhosis patients using unenhanced US, detection of liver metastases in patients with known primary malignancy, characterisation of incidentally detected FLLs visualised on unenhanced US, assessment of response to treatment in known liver malignancy) and further stratified by target condition (hepatocellular carcinoma [HCC], liver metastases, or 'any liver malignancy') and/or comparator test(s) (CECT, CEMRI, both), as appropriate. For all included studies, the absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals (CIs) were presented in results tables, for index test, comparator and target condition reported. Where multiple data sets were reported, (e.g., for per patient and per lesion data, different diagnostic criteria, different lesion sizes,) these were extracted in full. Data on the numbers of non-diagnostic tests were also included in the results tables and described in text summaries. No study reported data on patient preferences and one study reported absence of index test-associated adverse events; the latter was recorded in the relevant results table.

Where groups of similar studies (comparable clinical indication, index test and comparator, target condition and diagnostic criteria) included four or more data sets, The Assessment Group planned to construct summary receiver operating characteristic (SROC) curves and calculate summary estimates of sensitivity and specificity, with 95% CIs using the bivariate modelling approach; four data sets are the minimum requirement to fit models of this type. However, the review included only one group of four similar studies, and this group included one study which used a sub-

optimal reference standard. Pooled estimates of sensitivity and specificity, with 95% CIs, were therefore calculated using a random effects model and forest plots were constructed, showing the sensitivity and specificity estimates from each study together with pooled estimates. A sensitivity analysis was undertaken to assess the effect of excluding the large study which used a sub-optimal reference standard; these analyses were conducted using MetaDiSc 1.4.

Between study clinical heterogeneity was assessed qualitatively. Statistical heterogeneity was assessed, for the one meta-analysis undertaken, using the chi-squared test and inconsistency was quantified using the I^2 statistic, though these measures are of limited value given the small number of studies involved. There were no data sets of sufficient size (minimum ten) to allow statistical exploration of sources of heterogeneity by including additional co-variables in the SROC model.

Where meta-analysis was considered unsuitable for the data identified (e.g., due to the heterogeneity and/or small numbers of studies), studies were summarised using a narrative synthesis. Text and tables were stratified by clinical indication and target condition, as described above. Where appropriate, the results of individual studies were plotted in the receiver operating characteristics (ROC) plane.

See Section 4 in the DAR for more information on clinical effectiveness analysis.

Cost-effectiveness

Model Structure and Methodology

The health economic analysis assessed the value of CEUS in the following three populations:

- Detection of hepatocellular carcinoma through surveillance of patients with cirrhosis
- Detection of liver metastases in patients with colorectal cancer
- Characterisation of incidentally detected focal liver lesions

The comparators included the following liver imaging techniques:

- CECT
- Contrast enhanced magnetic resonance imaging using gadolinium as contrast agent (Gd-CEMRI)
- Contrast enhanced magnetic resonance imaging using superparamagnetic iron oxide as contrast agent (SPIO-CEMRI)

Three separate models were used to assess the cost-effectiveness of contrast enhanced ultrasound using the contrast agent SonoVue® in the populations specified above:

- A cirrhosis surveillance model
- A liver metastases of colorectal cancer model
- An incidentally detected FLL model

In all models the mean costs, life years gained and quality adjusted life years (QALYs) gained per patient were calculated for each comparator. Costs and benefits were discounted at 3.5%.

See Section 5 in the DAR for detailed information on each of the models mentioned above.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Developing Recommendations

After reviewing the evidence the Diagnostic Advisory Committee (DAC) agrees draft recommendations on the use of the technology in the National Health Service (NHS) in England. When formulating these recommendations, the Committee has discretion to consider those factors it believes are most appropriate to the evaluation. In doing so, the Committee has regard to any relevant provisions of the National Institute for Health and Care Excellence's (NICE's) Directions, set out by the Secretary of State for Health, and legislation on human rights, discrimination and equality. In undertaking evaluations of healthcare technologies, NICE takes into account the broad balance of clinical benefits and costs, the degree of clinical need of patients under consideration, any guidance issued to the NHS by the Secretary of State that is specifically drawn to the

attention of NICE by the Secretary of State, and any guidance issued by the Secretary of State, and the potential for long-term benefits to the NHS of innovation.

The Committee takes into account advice from NICE on the approach it should take to making scientific and social value judgements. Advice on social value judgements is informed in part by the work of NICE's Citizens Council.

The Committee takes into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: race, gender, disability, religion or belief, sexual orientation, gender reassignment and pregnancy or maternity.

The Committee considers the application of other Board-approved NICE methods policies, such as the supplementary guidance on discounting and the end-of-life criteria, if they are relevant to the evaluation.

Because the Programme often evaluates new technologies that have a thin evidence base, in formulating its recommendations the Committee balances the quality and quantity of evidence with the expected value of the technology to the NHS and the public.

The credibility of the guidance produced by NICE depends on the transparency of the DAC's decision-making process. It is crucial that the DAC's decisions are explained clearly, and that the contributions of registered stakeholders and the views of members of the public are considered. The reasoning behind the Committee's recommendations is explained, with reference to the factors that have been taken into account.

The language and style used in the documents produced by the Committee are governed by the following principles:

- Clarity is essential in explaining how the DAC has come to its conclusions.
- The text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This needs careful judgement so that enough information and justification is given in the recommendations to enable the reader to understand what evidence the DAC considered and, if appropriate, who provided that evidence.

The Committee may take into account factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the reference-case cost analysis, such as improved processes.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Cirrhosis Surveillance Model

Base-Case Cost-effectiveness Results

Contrast-enhanced ultrasound had the lowest discounted lifetime costs per person (£35,744), followed by contrast-enhanced computed tomography (CT) (£36,124) and contrast-enhanced magnetic resonance imaging (MRI) with gadolinium (£36,807). Compared with contrast-enhanced ultrasound, contrast-enhanced CT was as effective but more costly, and was thus considered to be dominated by contrast-enhanced ultrasound. Contrast-enhanced MRI with gadolinium cost £1063 more per person than contrast-enhanced ultrasound, but also yielded 0.022 more quality-adjusted life years (QALYs), giving an incremental cost-effectiveness ratio (ICER) of £48,454 per QALY gained.

Contrast-enhanced ultrasound is more cost-effective than contrast-enhanced MRI at £20,000 per QALY gained because although less effective it costs less and the ICER for contrast-enhanced MRI compared with contrast-enhanced ultrasound is above this value.

Investigating Potential Liver Metastases from Colorectal Cancer Model

Base-Case Cost-effectiveness Results

In the base-case analysis, using the different imaging techniques to investigate potential liver metastases from colorectal cancer resulted in equal expected lifetime QALYs (8.364). Contrast-enhanced ultrasound and contrast-enhanced CT were the least costly tests, with expected lifetime costs of approximately £7510 per person. Contrast-enhanced MRI with gadolinium (£7688) and contrast-enhanced MRI with superparamagnetic iron oxide (SPIO) (£7722) were both more costly than, and thus dominated by, contrast-enhanced CT and contrast-enhanced ultrasound.

Contrast-enhanced ultrasound and contrast-enhanced CT were cost-effective technologies, with equal expected costs and effectiveness.

Characterising Incidentally Detected Focal Liver Lesions

Base-Case Cost-effectiveness Results

The lower costs of contrast-enhanced ultrasound combined with slightly better test performance meant that contrast-enhanced ultrasound dominated both contrast-enhanced CT (contrast-enhanced ultrasound cost £52 less and yielded 0.0002 additional QALYs) and contrast-enhanced MRI (contrast-enhanced ultrasound cost £131 less and yielded 0.0026 additional QALYs).

Considerations

The Committee considered contrast-enhanced ultrasound with SonoVue for characterising incidentally detected focal liver lesions and noted that, in liver imaging, this clinical indication would likely be the most common application of the technology. The Committee noted that the base-case analysis showed clinically insignificant increases in effectiveness for contrast-enhanced ultrasound compared with contrast-enhanced CT and MRI. Moreover, there were cost decreases with contrast-enhanced ultrasound (£52 compared with contrast-enhanced CT, and £131 compared with contrast-enhanced MRI). Therefore, the Committee concluded that it could recommend contrast-enhanced ultrasound with SonoVue for characterising incidentally detected focal liver lesions.

The Committee considered contrast-enhanced ultrasound with SonoVue for characterising focal liver lesions identified through monitoring people with cirrhosis. The Committee considered the economic analysis performed by the External Assessment Group and noted that the base-case analysis showed that contrast-enhanced ultrasound with SonoVue was cost-effective. The Committee felt that the clinical evidence base was weaker for this indication.

See Sections 5 and 6 in the original guideline document for more information on cost-effectiveness.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The National Institute for Health and Care Excellence (NICE) sends the Diagnostics Assessment Report (DAR), with any confidential material removed, to registered stakeholders for comment. Stakeholders have 10 working days to return comments. Models supporting the DAR are made available to registered stakeholders on request during this period.

NICE presents anonymised registered stakeholder comments on the DAR, along with any responses from NICE or the External Assessment Group (EAG), to the Committee and later publishes these comments on its website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Diagnostics Advisory Committee considered clinical and cost-effectiveness evidence from a systematic review of contrast-enhanced ultrasound using SonoVue compared with contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) performed by an External Assessment Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Ultrasound scanning, along with other imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI), is important in diagnosing and planning treatment for many people with liver disease. Liver imaging sometimes identifies focal abnormalities that cannot be characterised initially and another test may be needed to further explore the abnormality. The main aim of subsequent liver imaging is to distinguish between cancer and benign abnormalities that are not likely to need further treatment.

Potential Harms

- Only 1 of the studies of test accuracy included in this assessment reported information on adverse events related to testing. In this study there were no adverse events associated with contrast-enhanced ultrasound with SonoVue. There was no information about the comparator (contrast-enhanced magnetic resonance imaging with gadolinium). A large, retrospective safety study of contrast-enhanced ultrasound with SonoVue in abdominal imaging did not meet the inclusion criteria for this assessment but reported data from 23,188 investigations in 29 centres in Italy. This study found 29 incidents of adverse events, of which 2 were graded as serious, 1 as severe, 3 as moderate and 23 as mild. There were no fatal adverse events. Most non-serious adverse events resolved without intervention.
- False-positive and false-negative results of contrast-enhanced ultrasound

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Care Excellence (NICE) has developed tools (see also the "Availability of Companion Documents" field), in association with relevant stakeholders, to help organisations put this guidance into practice. NICE will also support this guidance with a range of activities to promote the recommendations for further research. This will include incorporating the research recommendations in Section 7 in the original guideline document into the NICE guidance research recommendations database (available on the NICE website at www.nice.org.uk) and highlighting these recommendations to public research bodies. The research proposed will also be put forward to NICE's Medical Technologies Evaluation Programme research facilitation team for consideration of the development of specific research protocols.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). SonoVue (sulphur hexafluoride microbubbles) â€“ contrast agent for contrast-enhanced ultrasound imaging of the liver. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Aug. 41 p. (Diagnostics guidance; no. 5).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Aug

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Diagnostics Advisory Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are required to submit a declaration of interests on appointment, in every year of their tenure, and at each Committee meeting, in line with the National Institute for Health and Care Excellence's (NICE's) code of practice for declaring and dealing with conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .

Availability of Companion Documents

The following are available:

- Westwood ME, Joore MA, Grutters JPC, Redekop WK, Armstrong N, Lee K, Gloy VL, Raatz H, Misso K, Kleijnen J. Contrast enhanced ultrasound of the liver using SonoVue® (sulphur hexafluoride microbubbles): a systematic review and cost-effectiveness analysis. Diagnostics assessment report. York (UK): Kleijnen Systematic Reviews Ltd.; 2012. 282 p. Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2012. (Diagnostics guidance; no. 5). Electronic copies: Available from the NICE Web site .
- SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. Electronic audit tool. London (UK): National Institute for Health and Care Excellence (NICE); 2012. (Diagnostics guidance; no. 5). Electronic copies: Available from the NICE Web site .
- SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. Implementation advice based on practical experiences of using SonoVue. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Dec. (Diagnostics guidance; no. 5). Electronic copies: Available from the NICE Web site .
- Diagnostics Assessment Programme manual. London (UK): National Institute for Health and Care Excellence; 2011 Dec. 130 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- SonoVue (sulphur hexafluoride microbubbles) - contrast agent for contrast-enhanced ultrasound imaging of the liver. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Aug. (Diagnostics guidance; no. 5). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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